Multi-Gram Scale Synthesis of Chiral 3-Methyl-2,5-*trans*-tetrahydrofurans

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In this paper, we report the rapid and facile synthesis of chiral 3-methyl-2,5-*trans*-tetrahydrofurans. This reaction utilizes cheap and easily available starting materials. A domino hydrolysis and intramolecular Michael-type ring closure reaction was the key step. As a result, synthesis of the desired 3-methyl-2,5-*trans*-tetrahydrofurans could be achieved in gram-scale over 7 linear steps with high chemical yield and high diastereoselectivity.

Keywords: 3-methyl-2,5-*trans*-tetrahydrofurans; Ring closure; Gram-scale synthesis; Highly diastereoselective.

Introduction

3-Methyl-2,5-*trans*-tetrahydrofurans are critical structural elements for various natural products, biologically active compounds, and pharmaceuticals. [1−7] For instance, natural products chagosensine, [8, 9] cationomycin, [10, 11] amphidinolides C, C2, C3 and F [12−15] possesses such *trans*-tetrahydrofuran substructures. (Figure 1) As a consequence, many methodologies have been developed for the construction of this type of heterocycle. [16−22]

Among them, intramolecular conjugated addition of an oxygen nucleophile is often used for the formation of 3-methyl-2,5-*trans*-tetrahydrofurans (Scheme 1a), which inspired us to identify suitable conditions to obtain useful amount of 3-methyl-2,5-*trans*-tetrahydrofurans intermediates for further studies on total synthesis of natural products. [23, 24] Herein, we reported a rapid and facile process to access gram-scale quantities of 3-methyl-2,5-*trans*-tetrahydrofurans in just 7 linear steps. A domino hydrolysis and diastereoselective intramolecular Michael-type ring closure strategy is the key step (Scheme 1b).

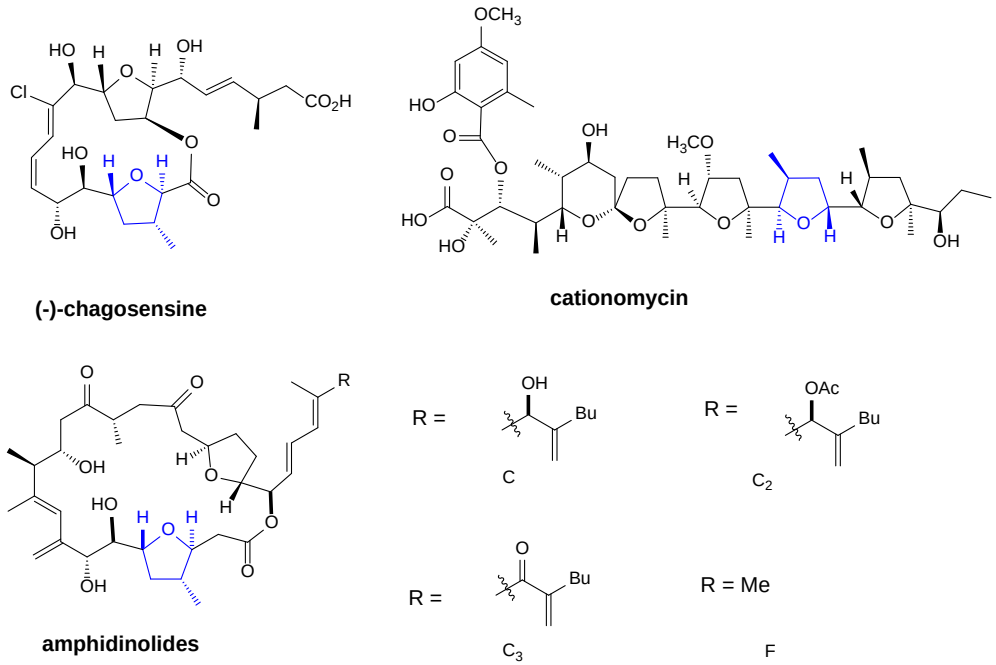
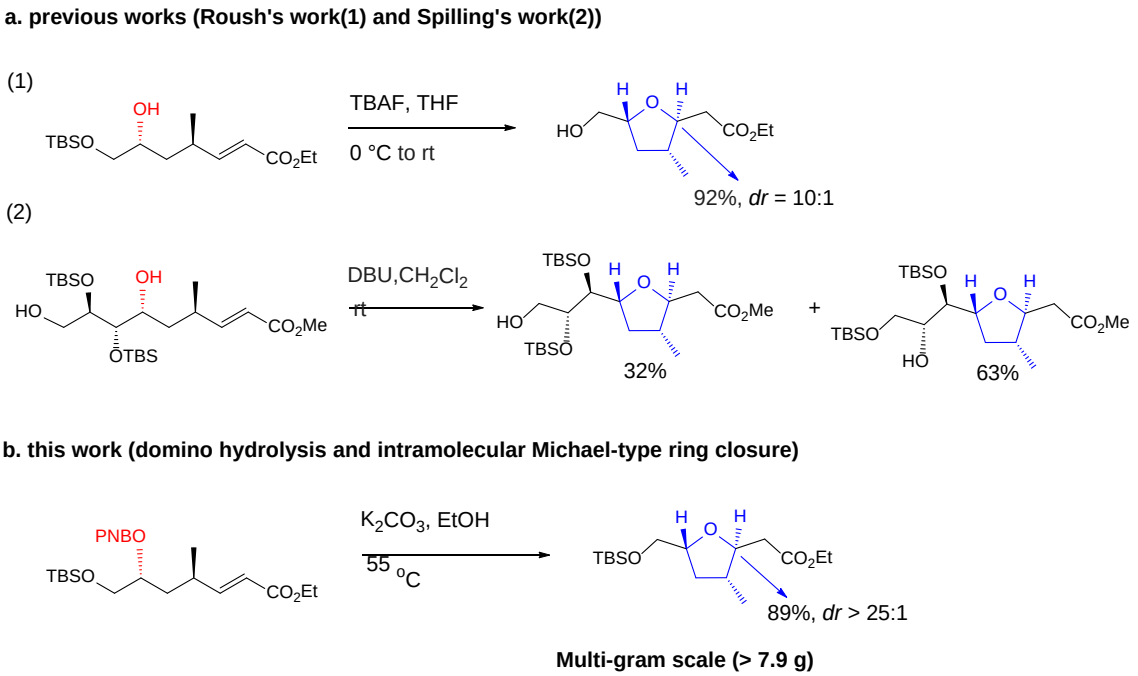


Figure 1. Representative natural products and bioactive compounds containing containing a 3-methyl-2,5-*trans*-tetrahydrofurans core.

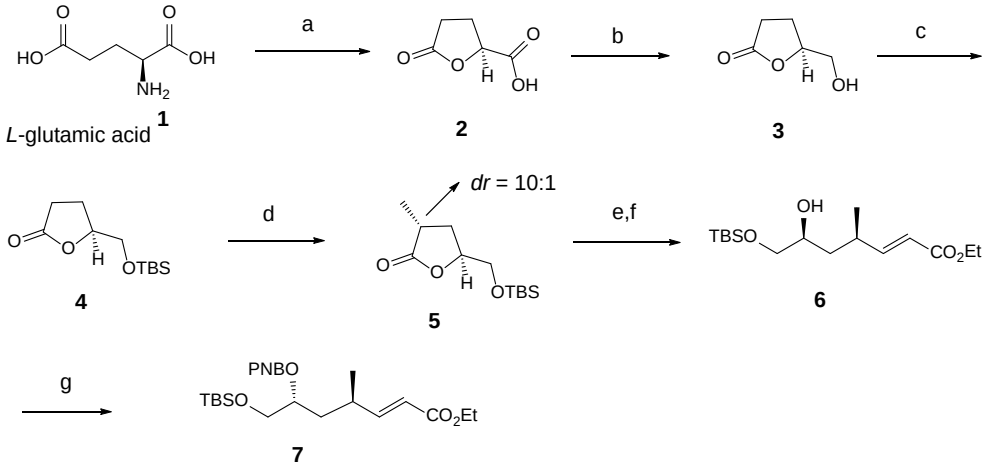


Scheme 1. Synthesis of 3-methyl-2,5-*trans*-tetrahydrofurans.

Results and Discussion

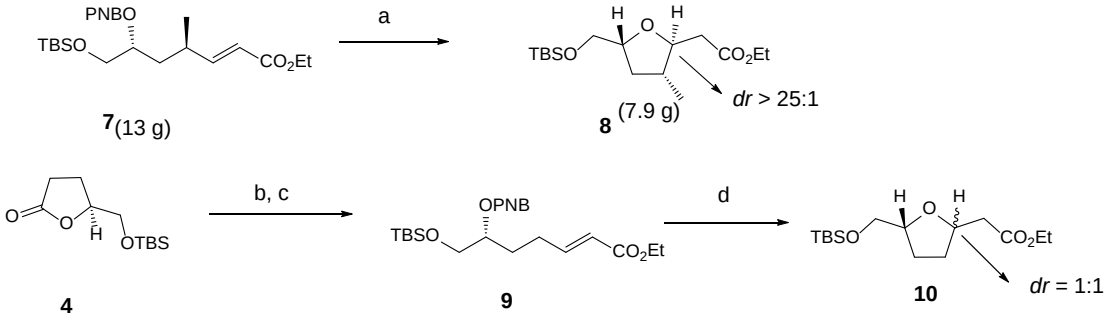
As depicted in Scheme 2, our synthetic route began with diazotization of inexpensive starting material, *L*-glutamic acid **1**, using $NaNO_2$ in HCl aqueous solution to provide lactone **2**. Reduction of the carboxyl group of lactone **2** with borane followed by protection of the primary alcohol **3** with TBSCl led to lactone **4**. Selective methylation of **4** using LiHMDS and MeI delivered **5** as a mixture of two diastereoiosmers (*dr* = 10:1). Although the two stereoiosmers of **5** could be separated by chromatography on silica gel, purification would be very time-consuming due to the similar polarity

of the two isomers. Hence, we used the mixture directly for the next step, and easy separation of isomeric products was performed at a later stage. With the mixture of two stereoisomers of **5** in hand, DIBAL reduction followed by Wittig reaction produced the pure conjugated ester **6** with an isolated yield over 85% of two steps. Subsequent mitsunobu reaction of hydroxyl group in **6** delivered PNB ester **7**.



Scheme 2. The synthesis of intermediate **7**. *Reagents and conditions:* **a** $NaNO_2$, HCl, H_2O, 0 °C to rt; **b** $BH_3{\cdot}SMe_2$, THF, 0 °C; **c** TBSCl, imidazole, DMAP, CH_2Cl_2, rt, 42% over 3 steps; **d** LiHMDS, MeI, THF, –78 °C, 80%; **e** DIBAL, –78 ºC; **f** $(Ph_3P)_3PCHCO_2Et$, PhMe, 80 °C, 85% over 2 steps; **g** Ph_3P, DIAD, *p*-nitrobenzoic acid, THF, 0 °C, 74% over 3 steps.

Following successful preparation of ester precursor **7**, the 3-methyl-2,5-*trans*-tetrahydrofuran **8** was formed through a domino hydrolysis and intramolecular Michael-type ring closure process using K_2CO_3 as base with multi-gram scale (7.9 g). Notably, the methyl-bearing stereogenic centre played a very important role in controlling the stereochemical outcome of the ring closure reaction (Scheme 3). Under the same conditions, the ester **10** was obtained from the cyclisation of **9**, which was synthesised from lactone **4** using the same synthetic route as described in scheme 2, but with no diastereocontrol (*dr* = 1:1).



Scheme 3. Domino hydrolysis and intramolecular Michael-type ring closure reaction. *Reagents and conditions:* **a** K_2CO_3, EtOH, 55 °C, 89%; **b** DIBAL, –78 ºC; **c** $(Ph_3P)_3PCHCO_2Et$, PhMe, 80 °C; **d** K_2CO_3, EtOH, 55 °C.

Conclusions

In summary, we have developed a domino hydrolysis and intramolecular Michael-type ring closure strategy to prepare 3-methyl-2,5-*trans*-tetrahydrofurans. It uses the readily-available chiral pool material L-glutamic acid as starting material. The required 3-methyl-2,5-*trans*-tetrahydrofuran was obtained with high chemical yield (18.8% overall yield) and high diastereoselectivity (*dr* > 25:1) over 7 steps. The process was also efficiently realized on multi-gram scale. Furthermore, the *trans*-tetrahydrofurans intermediate **8** can be subjected to further chain extension in either direction, which

might be useful for the synthesis of various natural products and biologically active compounds [25−29].

Supplementary Material

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/MS-number.

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Author Contribution Statement

S. Qin and Y. Cao contributed equally to this work. S. Qin, Y. Cao, and Y. Luo performed the experiments, analyzed the data. Prof. S. Jiang and Prof. J. S. Clark gave important suggestions for this project and help improved the language. Prof. X. Wang and Dr. G. Yang designed the experiments and wrote the manuscript.

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